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Effect of Ethanol and Vinyl Chloride on the Induction of Liver Tumors: Preliminary Report

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Preliminary results of a long-term animal study (rats) indicate synergism between inhaled vinyl chloride and ingested ethanol in tumorigenesis.

Introduction

A causal relationship between vinyl chloride and angiosarcoma of the liver is well documented in man (*1*) and in animals (*2*). However, little is known of factors which may influence the incidence of this rare form of cancer.

There is evidence indicating that alcohol dehydrogenase (*3*) and mixed function oxidase enzymes (*4*) of the liver metabolize vinyl chloride. Both of these enzymatic processes are also known to be stimulated by ethanol (*5, 6*). Such similarities in enzymatic activation suggest that ingestion of ethanol by a mammal may have an effect on the metabolism of vinyl chloride and induction of angiosarcoma in the liver.

Experimental Design

Three hundred and twenty Sprague-Dawley male rats were divided into four groups; all groups were fed Purina Rat chow. In addition, two groups received 5% ethanol in their water four weeks prior to the beginning of vinyl chloride inhalation and will continue to receive ethanol-water until death or sacrifice. Group designations and treatments are listed in Table 1. Groups IIIvc and IVvc-e were placed in individually compartmented stainless-steel holding cages for exposure by inhalation to 600 ppm vinyl chloride.

Table 1. Group designations and treatments.

Group	Number of animals	Diet	Inhalation protocol
I	80	Normal	Filtered air[a]
IIe	80	+ 5% Ethanol[b]	Filtered air[a]
IIIvc	80	Normal	600 ppm vinyl chloride[c]
IVvc-e	80	+ 5% Ethanol[b]	600 ppm vinyl chloride[c]

[a]Life of the animal.
[b]In water *ad libitum*.
[c]For 4 hr/day, 5 days/wk, 1 year.

Results

After 60 weeks, timed from the first exposure to vinyl chloride, 55 rats had died or had been sacrificed (265 living). At autopsy, a lesion was scored as a tumor only if it was encapsulated and larger than 1 cm in diameter. Observations made at autopsy indicate that the vinyl chloride-ethanol group developed more tumors in the liver than other groups (Table 2). Liver tumors occurred earlier and more frequently in the group of animals exposed to both vinyl chloride and ethanol (Fig. 1).

Histological examination of tissues has been completed of six vinyl chloride-exposed rats and seven vinyl chloride–ethanol-exposed rats (Table 3). Based on histological evidence, the latent period for angiosarcoma of the liver is 53 weeks in rats exposed by inhalation to 600 ppm vinyl chloride and 38 weeks

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in rats exposed to 600 ppm vinyl chloride and 5% ethanol.

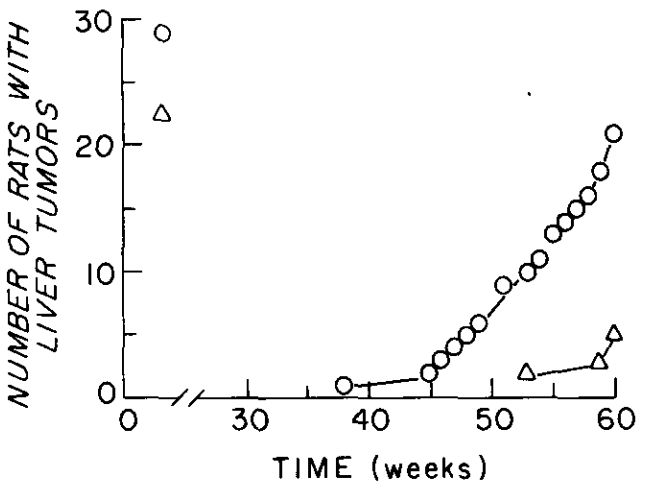

FIGURE 1. Time related to the first exposure of rats to vinyl chloride: (Δ) 600 ppm vinyl chloride; (O) 600 ppm vinyl chloride + 5% ethanol. Animals received 5% ethanol in water 4 weeks prior to vinyl chloride inhalation and will continue until death or sacrifice.

Discussion

These preliminary results clearly indicate synergism between ingested ethanol and inhaled vinyl chloride in the induction of tumors. Even though only 17% of the animals have been autopsied, a differential biological response is evidenced by latent periods and rates of tumorigenesis in the four groups.

In a long-term study, initial deaths are expected to occur among those animals most susceptible to the toxic effects of the administered agent or agents. For this reason it is quite possible that, in this study, complete data will reveal a smaller percentage of animals responding to the synergistic effects of vinyl chloride and ethanol.

These results suggest that data should be collected of the social and chronic drinking habits of workers exposed to hepatotoxic agents.

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Table 2. Sites of tumors observed at autopsy.

Group	Living	Dead	Rats with liver tumors	*Tumors observed at autopsy*[a]			
				Liver	Lung	Kidney	Other sites
I	72	8	0	0	0	0	0
IIe	74	6	0	0	0	1	1
IIIvc	67	13	5 (38%)	5	2	0	2
IVvc-e	52	28	21 (75%)	26	0	2	10

[a]Encapsulated and greater than 1 cm in diameter.

Table 3. Identification of cancerous lesions in 13 rats.

Group	Number of rats	Lesions at various sites			
		Liver[a]	Lung	Kidney	Other sites
IIIvc	6	Angiosarcoma (2)			Fibroma (1) (skin)
		Hepatocellular carcinoma (1)			
		Neoplastic nodules (1)			
IVvc-e	7	Angiosarcoma (5)	Angio-sarcoma (2)[b]	Angio-sarcoma (1)[c]	
		Hepatocellular carcinoma (2)		Fibro-sarcoma (1)	
		Neoplastic nodules (3)			

[a]Primary angiosarcoma.
[b]One primary, one metastasis.
[c]Metastasis.

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